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(54) Title: AMINOALKYL-BENZOFURAN-5-OL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

(57) Abstract: The present invention provides novel compounds, compositions containing the compounds of the invention in a
pharmaceutically acceptable excipient and methods for using the compositions for lowering intraocular pressure.

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AMINOALKYL-BENZOFURAN-5-OL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

5 BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to treatment for lowering intraocular pressure and to compounds for use in such treatments. More particularly, the present invention relates to the use of compounds with serotonergic 5-HT₅-HT₂ agonist activity to lower intraocular pressure (IOP), treat glaucoma, and to provide neuroprotection.

2. Description of the Related Art

Serotonin (5-hydroxy tryptamine; 5-HT/5-HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion 1992; Hoyer *et al.* 1994; Tobin *et al.* 1988].

20 5-HT is known to interact with at least seven major 5-HT receptors (5-HT₁ - 5-HT₇) and additional subtypes within these families to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer *et al.* 1994; Martin *et al.* 1998]. Receptor subtypes within the 5-HT₁ family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while 5-HT₄, 5-HT₆, and 5-HT₇ receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5-HT [Martin *et al.* 1998]. The receptors in the 5-HT₂ family are positively coupled to phospholipase C (PLC) and thus

generate inositol phosphates and mobilize intracellular calcium when activated to mediate the effects of 5-HT. The 5-HT₃ receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer *et al.* 1994].

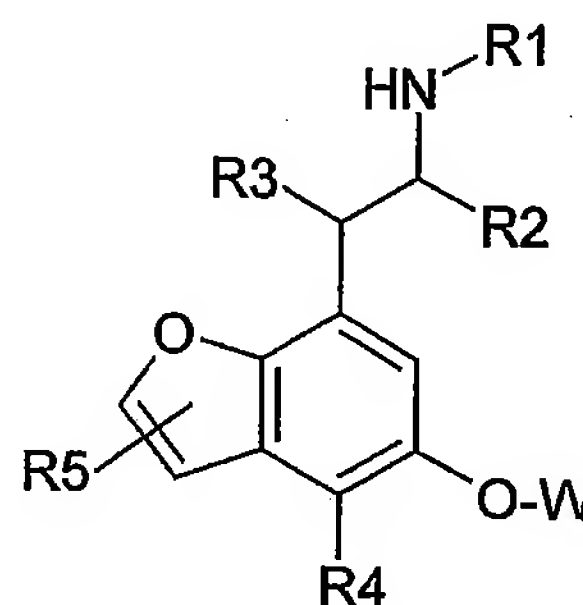
5 The human and animal 5-HT₇ receptor has only recently been cloned, expressed, and shown to be present in various brain areas and peripheral tissues [Eglen *et al.* 1997]. Recent studies have shown there to be four splice variants of the 5-HT₇ receptor [Heidmann *et al.* 1997]. It has been proposed that the 5-HT₇ receptor may be involved in the pathophysiology of sleep disorders, depression, and other psychiatric disorders [Eglen
10 *et al.* 1997]. In the periphery, stimulation of 5-HT₇ receptors results in relaxation of blood vessels and hence vasodilation [Eglen *et al.* 1997].

Known compounds exhibiting 5-HT₂ agonist activity have typically been designed to treat numerous central nervous system (CNS)-related conditions, particularly the
15 treatment of obesity and depression, by activation of 5-HT_{2C} receptors. Thus, one desired property of known 5-HT₂ agonist compounds is that they easily penetrate the blood brain barrier. Compounds possessing the property of penetration into the CNS generally do not contain polar groups.

20 To treat ocular diseases, it is desirable to administer compositions orally or topically that will remain in the ocular tissues and not cross the blood brain barrier to enter the CNS. What are needed are 5-HT₂ agonist compounds that are useful in the treatment of ocular diseases characterized by an elevated intraocular pressure, the treatment of glaucoma and neuroprotection. Such compounds would not have a propensity to cross the
25 blood brain barrier.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by
 5 providing compounds having 5-HT₂ agonist activity that do not cross the blood brain
 barrier. More specifically, the present invention provides compounds having the following
 general formula:



wherein R¹ is hydrogen or C₁₋₄alkyl; R² is hydrogen, C₁₋₄alkyl, or R¹ and R² can together be
 10 (CH₂)₂₋₄ to complete a heterocyclic ring; R³ is hydrogen, hydroxyl, C₁₋₄alkoxy, or fluorine;
 R⁴ is selected from C₁₋₄alkyl, halogen, nitrile, C₁₋₆alkylthiol, trifluoromethyl, C₁₋₄alkyl
 substituted by HO or C₁₋₃alkoxy, R⁵ is hydrogen, halogen, C₁₋₄alkoxy, nitrile, W is
 hydrogen or C(=O)C₁₋₈alkyl. In preferred embodiments, R¹, R³ and R⁵ are hydrogen, R² is
 methyl, R⁴ is halogen, methyl or trifluoromethyl, and W is hydrogen. Most preferably, the
 15 compounds of the invention have an R-configuration at the carbon atom bearing the
 primary amine.

In another aspect, the present invention provides compositions containing the
 compounds described above in a pharmaceutically acceptable excipient. The compositions
 20 are most preferably in the form of topical ophthalmic formulations for delivery to the eye.
 The compounds of the invention may be combined with ophthalmologically acceptable

preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution to form the compositions of the invention.

5 The compositions of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds of the invention as described above will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of .25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye
10 1 to 4 times per day according to the routine discretion of a skilled clinician.

The present invention further provides a method of lowering intraocular pressure in a mammal by administering to a patient in need thereof a therapeutically effective amount of a composition comprising a compound having the structure as described above in a
15 pharmaceutically acceptable excipient. In preferred embodiments, the composition can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant).

DETAILED DESCRIPTION PREFERRED EMBODIMENTS

20

It has been found that serotonergic compounds which possess agonist activity at 5-HT₂ receptors effectively lower and control elevated IOP and glaucoma. Serotonergic nerves innervate the eye [Tobin *et al.* 1988] and 5-HT has been found in the aqueous humor of human eyes [Martin *et al.* 1988]. In addition, receptor binding sites for [³H]5-HT have been demonstrated and pharmacologically characterized in the iris-ciliary body
25

(ICB) of rabbits [Mallorga and Sugrue 1987; Chidlow *et al.* 1995]. These 5-HT binding sites have been shown to be functionally coupled to second messenger generation in rabbits [Tobin and Osborne 1989; Tobin *et al.* 1988]. In the human ICB these binding sites are characterized as 5-HT_{1A} and 5-HT₂ receptors [Barnet and Osborne 1993]. In addition, 5 the presence of mRNAs for 5-HT_{1A} and 5-HT₇ receptors in the rabbit ICB have been reported [Chidlow *et al.* 1995; Osborne and Chidlow 1996]. The precise functions of these receptors in the eye are unknown, especially the 5-HT₇ subtype(s).

5-HT or 5-carboxamidotryptamine (5-CT) topically applied to the rabbit eye raise 10 intraocular pressure in the anterior chamber of the eye [Meyer-Bothling *et al.* 1993]. By contrast, it has been shown that topically applied 5-HT lowers IOP [Krootila *et al.* 1987 (intracamerally 5-HT raised IOP and caused breakdown of the blood-aqueous barrier)]. In addition, the 5-HT uptake inhibitor, fluoxetine (Prozac®), also raises IOP in human subjects upon oral administration [Costagliola *et al.* 1996] and may cause glaucoma 15 [Ahmad 1992]. However, the 5-HT receptor subtype(s) involved in the IOP-elevating effects of 5-HT, 5-CT and fluoxetine are unknown.

Studies conducted in rabbits with 8-hydroxy DPAT and MKC-242 (5-HT_{1A} agonists) have shown these compounds lower IOP [Osborne and Chidlow 1996; EP 20 0771563-A2]. In addition, 5-methylurapidil (5-HT_{1A} agonist) lowered IOP in glaucomatous monkeys [Wang *et al.* 1997]. Both MKC-242 and 5-methylurapidil are relatively potent α 1 receptor antagonists (α 1 antagonists are known to lower IOP in rabbits, monkeys, and man). The mechanism of action for lowering IOP by 5-methylurapidil has been attributed to its α 1 antagonist activity and not its 5-HT_{1A} agonist

activity [Wang *et al.* 1998]. U.S. Patent No. 5,693,654, discloses 5-HT₁ receptor agonists for lowering IOP. WO 92/20333 discloses certain 5-HT_{1A} agonists for the treatment of glaucoma.

5 Methysergide (5-HT₂ antagonist) lowered IOP in rabbits [Krootila *et al.* 1987]. Ketanserin (5-HT_{2A/C} antagonist), also with significant α 1 antagonist activity, lowers IOP in rabbits and man [Chan *et al.* 1985; Costagliola *et al.* 1991]. Saprogrelate (5-HT_{2A} antagonist) lowers IOP in rabbits and in man when dosed topically or orally [Mano *et al.* 1995; Takenaka *et al.* 1995]. EP 522226 and U.S. Patent No. 5,290,781 disclose the use
10 of ketanserin and its derivatives for treating ocular hypertension. U.S. Patent Nos. 5,290,781 and 5,106,555 discloses the use of certain 5-HT₂ antagonists for lowering IOP. U.S. Patent No. 5,652,272 discloses saprogrelate for reducing IOP. U.S. Patent No. 5,538,974 discloses ophthalmic compositions of certain 5-HT₂ antagonists for lowering IOP,

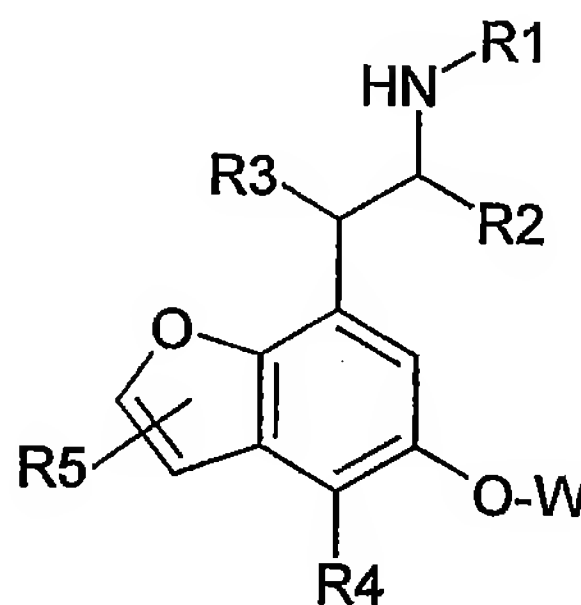
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U.S. Patent No. 5,011,846 discloses certain 5-HT₃ receptor antagonists for treating glaucoma.

WO 97/17345 discloses that particular compounds with 5-HT₄ serotonergic
20 receptor agonist or antagonist activity are useful for treating psychiatric, gastrointestinal, lower urinary, and cardiovascular disorders. The publication mentions the compounds may also be useful for glaucoma.

The present inventor has discovered that compounds with the general formula (I) have 5-HT₂ agonist activity and may be useful in lowering IOP, treating glaucoma, and/or provide neuroprotection for retinal ganglion cells.

5 **Formula (I)**



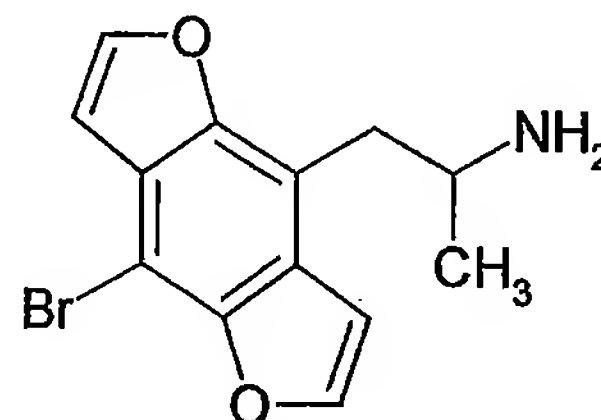
In Formula I, R¹ is hydrogen or C₁₋₄ alkyl; R² is hydrogen, C₁₋₄alkyl, or R¹ and R² together can be (CH₂)₂₋₄ to complete a heterocyclic ring; R³ is hydrogen, hydroxyl, C₁₋₄alkoxy, or fluorine; R⁴ is selected from C₁₋₄alkyl, halogen, nitrile, C₁₋₆alkylthiol, trifluoromethyl, C₁₋₄alkyl substituted by HO or C₁₋₃alkoxy, R⁵ is hydrogen, halogen, C₁₋₄alkoxy, nitrile and W is hydrogen or C(=O)C₁₋₈alkyl.

The compounds of the invention will preferably possess the following properties:

- 15 1) agonist activity at the 5-HT₂ receptors, and 2) significantly greater chemical stability than serotonin, the endogenous receptor ligand.

D.E. Nichols and colleagues at Purdue University have developed a number of benzofuran- and benzodifuranyl-alkylamines over the past decade and have demonstrated their affinity and efficacy at the 5-HT_{2A} receptor as well as their hallucinogenic activity as

evaluated in animals. Dr. Nichols' focus has been on the development of compounds with CNS activity, that is, that readily cross the blood brain barrier. Thus, these known compounds are outside of the scope of the compounds encompassed by Formula I above.

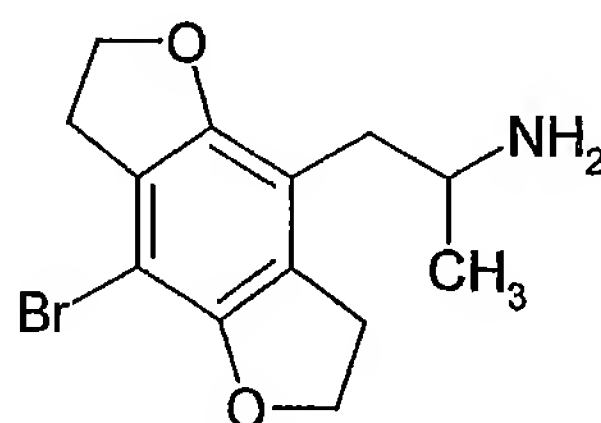


For example, Nichols has developed a compound with the following structure (compound
5 1) (Parker *et al.* 1998).

Compound 1

The Nichols compound has been shown to have a high affinity for the 5-HT_{2A} receptor and to generalize to LSD in drug discrimination studies. Nichols and colleagues
10 also studied compounds in the class of that shown below (compound 2) for CNS activity.

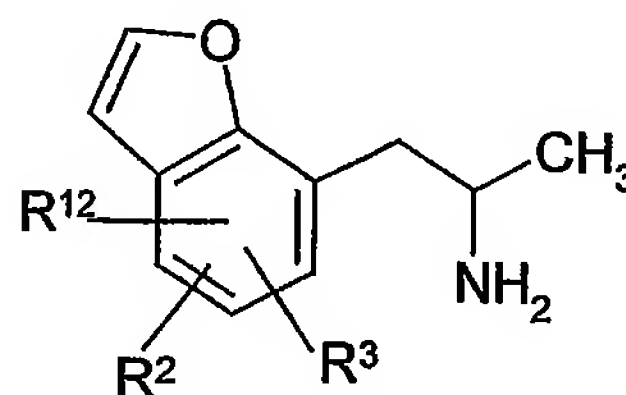
Compound 2



(Monte *et al.* 1996). Neither of the compounds studied by Nichols and colleagues is within the scope of the present invention. Furthermore, Nichols does not discuss use of
15 compounds 1 or 2 for the treatment of any ocular diseases, ocular hypertension or glaucoma. The goal in creating compounds 1 and 2 was to produce compounds useful for CNS disorders and such compounds would necessarily have to have the ability to penetrate

the blood brain barrier. In contrast, the compounds of the present invention are designed not to cross the blood brain barrier but to remain in the ocular tissue.

Eli Lilly developed a series of benzofuran compounds that are similar to the
5 compounds of Formula I herein. (WO 00/44737). Lilly's compounds have the following general formula:



These compounds are described as having utility for numerous CNS-related conditions, particularly the treatment of obesity and depression by activation of 5-HT_{2C}
10 receptors. Thus, it is desirable that these compounds would penetrate into the brain. None of the compounds described in Lilly come within scope of the present invention. The compounds of the invention are designed to avoid penetration into the brain whereas the Lilly compounds are specifically aimed at crossing the blood brain barrier in order to treat CNS diseases.

15

The compounds of the invention have a low propensity to enter the CNS, or to cross the blood brain barrier, due to the presence of the highly polar hydroxyl group. Thus, the compounds of the invention are less likely to elicit undesirable centrally mediated side effects, such as those associated with the CNS active compounds described
20 by Nichols and Lilly. The preferred 4-substituted 7-(2-aminopropyl)-benzofuran-5-ol

compounds of Formula I have a greater chemical stability than serotonin or other indole analogs.

The compounds of the invention may be prepared by known synthetic procedures,
5 such as those reported in WO 00/44737, and other well known synthetic transformations.

The compounds of the invention can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant). The compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The compounds
10 may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable
15 surfactant to assist in dissolving the compound. Additionally, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and
20 xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination

of, for example, carbopol-940, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The compounds of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of .25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician.

10

The compounds can also be used in combination with other IOP lowering agents, such as, but not limited to, β -blockers, prostaglandins, carbonic anhydrase inhibitors, α_2 agonists and miotics. The compounds can also be used in combination with other agents useful for treating glaucoma, such as, but not limited to, calcium channel blockers and NMDA antagonists. These agents may be administered topically, but usually systemically.

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both

chemically and structurally related may be substituted for the agents described herein to achieve similar results. All such substitutions and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

5

References

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

10

United States Patents

5,011,846

5,106,555

5,290,781

15

5,538,974

5,652,272

5,693,654

Foreign Patents and Published Applications

EP 0771563-A2

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EP 522226

WO 92/20333

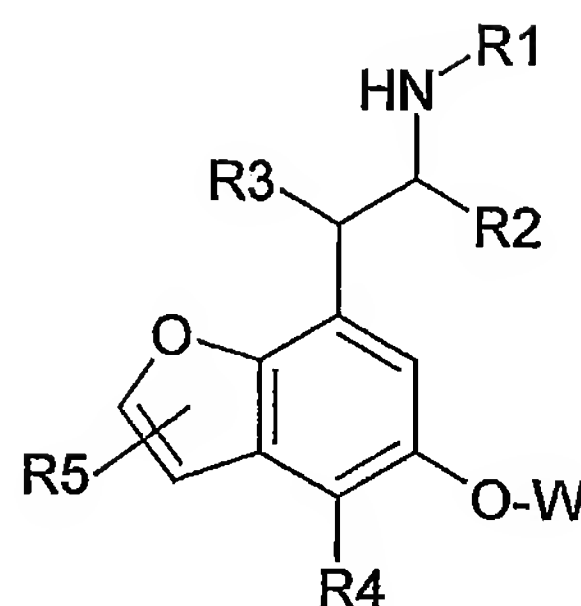
WO 97/17345

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We Claim:

1. A compound having the structure as follows:



5 wherein R¹ is hydrogen or C₁₋₄alkyl; R² is hydrogen, C₁₋₄alkyl, or R¹ and R² can together be (CH₂)₂₋₄ to complete a heterocyclic ring; R³ is hydrogen, hydroxyl, C₁₋₄alkoxy, or fluorine; R⁴ is selected from C₁₋₄alkyl, halogen, nitrile, C₁₋₆alkylthiol, trifluoromethyl, C₁₋₄alkyl substituted by HO or C₁₋₃alkoxy, R⁵ is hydrogen, halogen, C₁₋₄alkoxy, nitrile, W is hydrogen or C(=O)C₁₋₈alkyl.

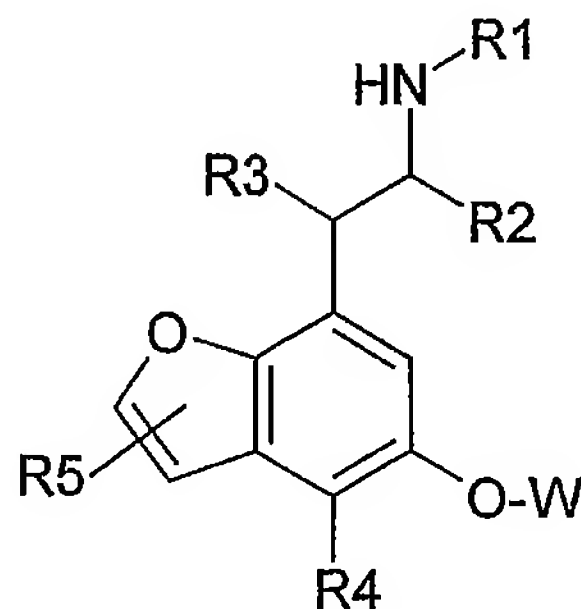
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2. The compound of claim 1, wherein R¹, R³ and R⁵ are hydrogen, R² is methyl, R⁴ is halogen, methyl or trifluoromethyl, C₁₋₄alkyl substituted by HO or C₁₋₃alkoxy, and W is hydrogen.

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3. The compound of claim 2, further defined as the stereoisomer with an R-configuration at the carbon atom bearing the primary amine.

4. A composition comprising at least one compound having the structure as



follows and a pharmaceutically acceptable excipient:

wherein R¹ is hydrogen or C₁₋₄alkyl; R² is hydrogen, C₁₋₄alkyl, or R¹ and R² can together be (CH₂)₂₋₄ to complete a heterocyclic ring; R³ is hydrogen, hydroxyl, C₁₋₄alkoxy, or fluorine;
5 R⁴ is selected from C₁₋₄alkyl, halogen, nitrile, C₁₋₆alkylthiol, trifluoromethyl, C₁₋₄alkyl substituted by HO or C₁₋₃alkoxy, R⁵ is hydrogen, halogen, C₁₋₄alkoxy, nitrile, W is hydrogen or C(=O)C₁₋₈alkyl.

5. The composition of claim 4, wherein the compound is further defined as
10 follows: R¹, R³ and R⁵ are hydrogen, R² is methyl, R⁴ is halogen, methyl or trifluoromethyl, C₁₋₄alkyl substituted by HO or C₁₋₃alkoxy, and W is hydrogen.

6. The composition of claim 5, wherein the compound is further defined as the stereoisomer with an R-configuration at the carbon atom bearing the primary amine.
15

7. The composition of claim 4, further comprising ophthalmologically acceptable preservatives.

8. The composition of claim 4, further comprising ophthalmologically
20 acceptable surfactants.

9. The composition of claim 4, further comprising an agent to increase viscosity.

25 10. The composition of claim 9, wherein the agent is selected from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and polyvinylpyrrolidone.

11. The composition of claim 4, further comprising ophthalmologically
30 acceptable preservatives, ophthalmologically acceptable surfactants and at least one agent to increase viscosity.

12. The composition of claim 4, further defined as a topical ophthalmic suspension or solution having a pH of about 5 to about 8.

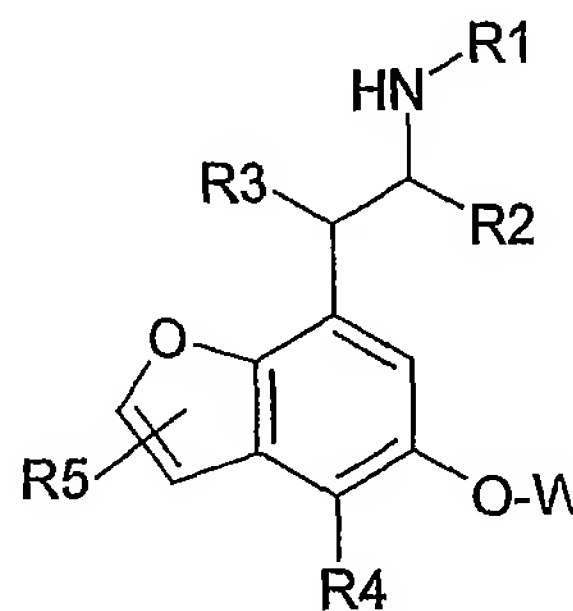
13. The composition of claim 12, wherein the concentration of the compound is
5 from .01% to 5% by weight.

14. The composition of claim 13, wherein the composition of the compound is from .25% to 2% by weight.

10 15. The composition of claim 4, further comprising at least one agent selected from the group consisting of β -blockers, prostaglandins, carbonic anhydrase inhibitors, α_2 agonists and miotics.

16. The composition of claim 4, further comprising at least one agent selected
15 from the group consisting of calcium channel blockers and NMDA antagonists.

17. A method of lowering intraocular pressure in a mammal, said method comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising a compound having the structure as follows:



20

wherein R^1 is hydrogen or C_{1-4} alkyl; R^2 is hydrogen, C_{1-4} alkyl, or R^1 and R^2 can together be $(CH_2)_{2-4}$ to complete a heterocyclic ring; R^3 is hydrogen, hydroxyl, C_{1-4} alkoxy, or fluorine; R^4 is selected from C_{1-4} alkyl, halogen, nitrile, C_{1-6} alkylthiol, trifluoromethyl, C_{1-4} alkyl substituted by HO or C_{1-3} alkoxy, R^5 is hydrogen, halogen, C_{1-4} alkoxy, nitrile, W is
25 hydrogen or $C(=O)C_{1-8}$ alkyl.

18. The method of claim 17, wherein R^1 , R^3 and R^5 are hydrogen, R^2 is methyl, R^4 is halogen, methyl or trifluoromethyl, C_{1-4} alkyl substituted by HO or C_{1-3} alkoxy, and W is hydrogen.

5

19. The method of claim 18, wherein the compound is further defined as the diastereomer with an R-configuration at the carbon atom bearing the primary amine.

20. The method of claim 17, wherein the composition is in the form of a topical
10 ophthalmic suspension or solution.

21. The method of claim 17, wherein the composition is administered by topical application to the eye.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/38908

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A 61K 31/34; C07D 307/81, 307/82

US CL : 514/469; 549/462, 471

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/469; 549/462, 471

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, WEST, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/44737 A1 (ELI LILY AND COMPANY) 03 AUGUST 2000 (03/08/2000) whole document and compounds of formula 1.	1-6
Y	US 5,539,974 A1 (OGAWA et al) 23 July 1996 (23/07/1996) column 7 and 8 lines 30-68 and 1-68, opthalmic composition compositions.	1-21
X	Database CAPLUS on STN, AN 1984:68106, GRINEV et al. "Synthesis of 4,5-dihydroxy-7-2(2-aminopropyl)- and 4,5, dihydroxy-7(2-phenyl-2-aminoethyl)benzofuran derivatives', abstract, 1983.	1-3



Further documents are listed in the continuation of Box C.



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Date of the actual completion of the international search

03 February 2003 (03.02.2003)

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